Receptor-Receptor Interactions and Their Relevance for Receptor Diversity

Focus on Neuropeptide/Dopamine Interactions[a]

K. FUXE,[b,c] X.-M. LI,[b] S. TANGANELLI,[d] P. HEDLUND,[b]
W. T. O'CONNOR,[e] L. FERRARO,[d] U. UNGERSTEDT,[e]
AND L. F. AGNATI[f]

[b]*Department of Neuroscience*
[e]*Department of Physiology and Pharmacology*
Karolinska Institutet
Stockholm, Sweden

[d]*Department of Pharmacology*
University of Ferrara
Ferrara, Italy

[f]*Department of Human Physiology*
University of Modena
Modena, Italy

Receptor diversity appears to be a general phenomenon occurring for both G-protein–coupled and ion channel–coupled receptors involved in neuronal communication. In our own work we analyzed the role of receptor diversity in the dopamine (DA) receptor systems of the basal ganglia.[1–5] Five subtypes of DA receptors exist, namely, D_1 to D_5. The two major DA receptor subtypes are the D_1 receptors, which by activation of the G_s-proteins increase adenylate cyclase activity and phospholipase C activity, and the D_2 receptors which, via G_i-proteins, are coupled to multiple transduction pathways involving inhibition of adenylate cyclase and phospholipase C activity, regulation of calcium influx, opening of potassium channels, and increases of arachidonic acid release.[6,7]

This paper introduces the hypothesis that one meaning of receptor diversity is that it allows the development of discrete interactions between receptor subtypes of the same transmitter as well as for different transmitters, leading to the development of a new type of plasticity in synaptic (wiring) transmission (WT) and volume transmission (VT).[8]

POSSIBLE FUNCTIONAL MEANING OF RECEPTOR DIVERSITY

Multiple reasons probably exist for the development of a high degree of receptor diversity in large numbers of receptor systems for the transmitters of the nervous system. In the case of G-protein–coupled receptors, it seems likely that the receptor

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[c]Address correspondence to Prof. Kjell Fuxe, Department of Neuroscience, Division of Cellular and Molecular Neurochemistry, Karolinska Institutet, 171 77 Stockholm, Sweden.

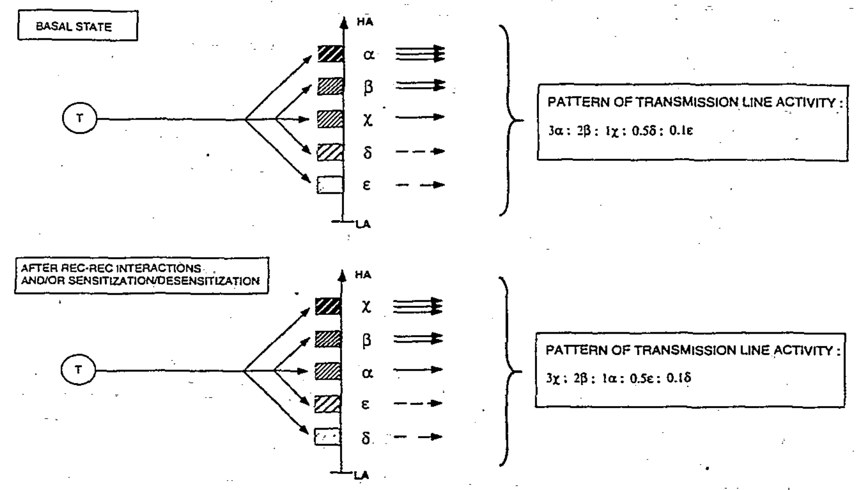

FIGURE 1. Schematic representation of the possible role of receptor-receptor interactions in the pattern of subtype receptor (α, β, γ, . . .) activation. The scheme is based on the following conditions: (1) equal amount of transmitter (T) released in the basal state and after receptor-receptor interactions or sensitization/desensitization; (2) equal receptor subtype densities; and (3) equal access of T to the various receptor subtypes. Note that basal state can probably be observed only *in vitro*.

diversity allows the receptors to couple to different types of G-proteins, which leads to the activation or inhibition of multiple transduction mechanisms as is the case, for example, for the DA receptor family. Because of such multiple transduction mechanisms it becomes possible for the transmitter, DA, for example, to increase the flow of information over the synapses. Instead, in the case where the receptor subtypes have the same transduction mechanism, the existence of the receptor subtypes allows the redundancy of the transmission so that the safety of the transmission processes can be insured.

The existence of receptor subtypes with a relatively high and a relatively low affinity for the transmitter—for example DA—makes it possible to have a transmission process with very low release of the transmitter, and also to recruit, with increasing impulse flow, new receptor subtypes having a higher affinity for the transmitter, but located further away from the site of release.

By recruiting in the transmission process different receptor subtypes such as D_1 and D_2 receptors, it also becomes possible to develop positive or negative cooperation between the receptor subtypes.[9] As an example, the DAergic inhibition of the sodium potassium ATPase requires the recruitment of both D_1 and D_2 receptors.[10] It may also be surmised that whereas low-affinity receptors can be involved in the WT, high-affinity receptors may also be involved in the VT.

The existence of receptor diversity makes possible the development of receptor subtype-specific interactions with other transmitter receptors so that the plasticity of transmission can be substantially increased (FIG. 1). Thus, by selectively antagonizing the transduction over the D_2 receptor subtype, transmission over the D_1 receptor subtype will be favored,[11] as illustrated in the selective heteroregulation of D_2 receptors by neurotensin (NT) receptors. Other selective regulators of D_2 receptors

are the cholecystokinin (CCK) A and B receptors.[12–15] A powerful antagonistic regulator specifically involved in the inhibitory control of D_2 receptor transduction is adenosine operating via A_{2a} receptors.[16] It should be noted that, unlike the neuropeptides, the A_{2a} receptors not only can control the modulation within an affinity state but can also trigger a switching in the proportion of the two affinity states (FIG. 2).

Another functional meaning of receptor diversity is probably also the possibility to desensitize or sensitize the various receptor subtypes for one receptor in a differential manner. This may be brought about either via the second messenger mechanisms involving protein phosphorylation of the receptor subtype proteins, but could also involve the receptor-receptor interactions within the membrane. Thus, it seems possible that neuropeptide receptors, such as the NT and the CCK_A and CCK_B receptors can modulate the desensitization process via the regulation and modulation of receptor affinities. Such phenomena will be capable of regulating the duration of the postsynaptic responses induced by the transmission process.

Thus, it seems clear that the receptor diversity in combination with receptor-receptor subtype specific interactions, which can be antagonistic or synergistic in character, markedly increase plasticity in WT and VT in the nervous system. In this way, switching among transmission lines for the various DA receptor subtypes will become possible. Thus, both the peak and the duration of the transmission process

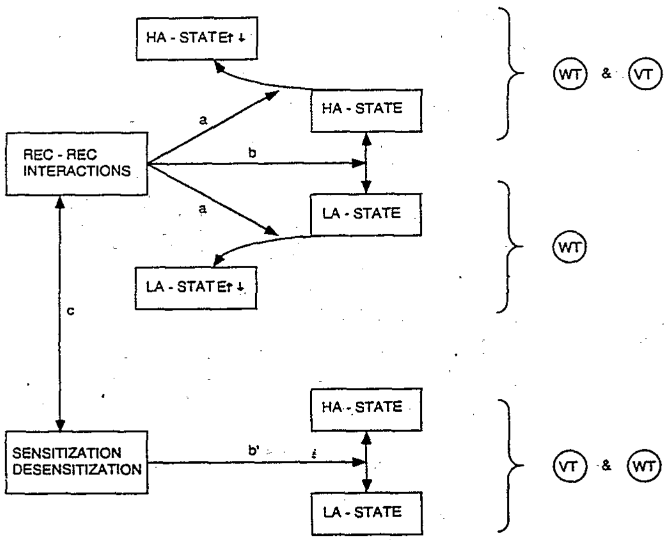

FIGURE 2. Schematic representation of the possible role of receptor-receptor interactions and sensitization/desensitization in the control of receptor affinity. It should be observed that receptor-receptor interactions can modulate both receptor affinity within an affinity state (**a**), as well as trigger the switch in the proportion between the two different affinity states (**b**). Also indicated in the scheme is that sensitization/desensitization processes can affect receptor-receptor interactions (**c**), as well as switch the receptor affinity from the high-affinity (HA) to the low-affinity (LA) state and vice versa (**b'**). The preferential role of the affinity state of a receptor for volume transmission (VT) and wiring transmission (WT) is also indicated. For further details, see text.

can become substantially modulated in relation to the state of activity of the target neuron and its other afferent inputs.

Some of these aspects are supported by our work on selective modulation of D_2 receptors by CCK and NT. In this paper we will illustrate how such receptor subtype-specific interactions among receptors can represent a substrate of neuronal plasticity.

SELECTIVE REGULATION OF D_2 RECEPTORS VIA CCK RECEPTOR SUBTYPES AND NEUROTENSIN RECEPTORS MAY UNDERLIE CCK/DOPAMINE AND NEUROTENSIN/DOPAMINE INTERACTIONS IN THE BASAL GANGLIA

Studies at the Membrane Level

It was early demonstrated that an antagonistic intramembrane regulation of postsynaptic striatal D_2 receptors by CCK receptors may exist that may underlie the neuroleptic-like actions found after central CCK-8 administration.[12,13,15,17–19] The results obtained in striatal membranes, both from the dorsal and ventral part, demonstrated that CCK-8 could produce a selective reduction of the D_2 agonist affinity without any change in the B_{max} value. Recently, it has been shown by Li *et al.*[15] that 0.1 nM of CCK-8 increases the K_d value of the D_2 agonist [^{3}H]N-propylnor-apomorphine (NPA) binding sites by 42%, an action blocked by the CCK_B antagonist PD134308. This increase in the K_d value by CCK-8 was probably related to a reduction of the association rate constant of [^{3}H]NPA by 45% induced by CCK-8. In contrast, NT, which also has been found to increase the K_d value of the D_2 agonist binding sites, did so instead by increasing the dissociation rate constant.[20] The fact that CCK-8 reduces the association rate constant[15] whereas NT increases the dissociation rate constant in their modulation of the K_d value of the D_2 agonist binding sites may explain the recent observation of synergistic interactions between NT and CCK-8 in their inhibitory control of D_2 receptors.[21] A synergistic interaction was not obtained when a high concentration of the neuropeptides was used, suggesting that the two types of neuropeptide receptors can interact with a common regulatory mechanism in the D_2 receptor transduction.

It should be underlined that only the CCK_B receptors are involved in the reduction of the K_d value of the D_2 agonist binding sites in rat striatal membranes, inasmuch as the CCK_A antagonist L364718 was ineffective in counteracting the increase of the K_d value by 1 nM of CCK-8.[15] These results are also in line with the early studies of Agnati, Fuxe, and colleagues that also CCK-4, a selective CCK_B agonist, reduces the affinity of the D_2 agonist binding sites in striatal membranes.[12,13] Thus, it seems clear that a receptor subtype of the CCK receptor family, the CCK_B receptor subtype, can selectively interact in an inhibitory way with the D_2 receptor subtype of the DA receptor family, illustrating the receptor subtype selectivity involving both the interacting receptors. However, it must be emphasized that the D_3 and D_4 subtypes of DA receptors have not yet been tested for their interaction with the CCK and NT receptors, so that the absolute specificity of these interactions still remains to be clarified. It is of substantial interest that the C-terminal NT-(8–13) fragment potently and antagonistically modulates rat neostriatal D_2 receptors[22] and that neuromedin N (NN) also is a potent modulator of D_2 receptor agonist binding in rat neostriatal membranes.[23] In view of the higher potency of NN versus NT to regulate neostriatal D_2 receptors—in contrast to the higher potency of NT versus NN to bind to the cloned NT receptors—the NN-activated neostriatal NT, receptors

involved in the regulation of the D_2 receptors, may represent a distinct subtype of NT receptors.[23]

However, in competition experiments a different type of modulation of D_2 receptors by CCK-8 has been observed.[15] CCK-8 (1 nM) was found to reduce the K_H and K_L values of DA for the D_2 antagonist [^{3}H]raclopride binding sites in the order of 50% (FIG. 3). These increases in affinity were found to be blocked by both CCK_A and CCK_B antagonists. Of substantial interest was the demonstration that the D_1 antagonist SCH23390 counteracted the CCK-8–induced reductions in the K_H and K_L values of DA. Thus, it seems clear that upon a joint activation of D_1 and D_2 receptors, CCK-8 via activation of both CCK_A and CCK_B receptors, will increase and not reduce the affinity of D_2 receptors for DA. The pattern of DA receptor subtype activation will determine whether CCK-8 will antagonize or enhance D_2 receptor

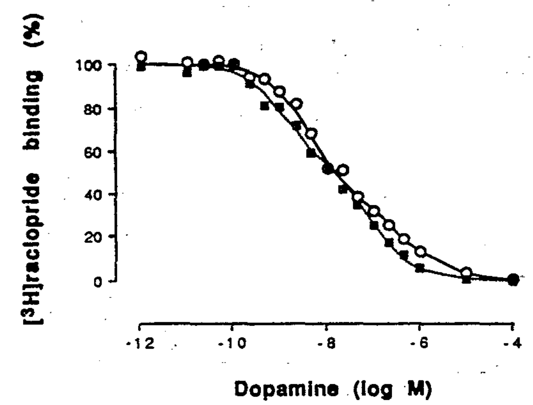

FIGURE 3. Representative competition curves illustrating the effect of 1 nM of cholecystokinin octapeptide (CCK-8) on dopamine (DA)-induced inhibition of D_2 antagonist [^{3}H]raclopride (2 nM) binding in rat neostriatal membranes. Competition experiments with 20 concentrations of DA (1 pM–0.1 mM) were performed by incubating the neostriatal membranes for 30 min at 25 °C in the presence of 1 nM of CCK-8. Using iterative nonlinear regression fitting procedure, the K_H and the K_L values were 4.10 nM and 284 nM, respectively, for the control curve (O), and 1.17 nM and 92 nM, respectively, for the 1 nM of CCK-8 curve (■). The R_H values were 51 and 46%, respectively.

transduction within the brain. It appears that especially the D_1 receptor exerts a switching action in D_2 regulation, so that upon D_1 receptor activation CCK-8 then enhances the affinity of the D_2 receptors instead of reducing it. Thus, the pattern of DA receptor subtype activation will determine the type of modulation of the D_2 receptors induced by activation of CCK receptor subtypes. This view has recently been strengthened by observations that CCK-8 *in vitro* and *in vivo* can strongly regulate striatal D_2 receptors in sections of rat forebrain in the same way as observed in the striatal membrane preparations.[24] Of particular interest in this analysis was the demonstration by Li *et al.*[24] that a stronger CCK/DA interaction was found in sections versus that found in membrane preparations, indicating that either cytosolic factors and/or intact membranes are necessary for the full development of this type of receptor interaction. Another interesting finding was the demonstration that

within the CCK/DA costoring region of the nucleus accumbens a stronger modulation of D_2 receptor binding characteristics was found to take place after the *in vitro* and *in vivo* treatment with CCK-8. Therefore, these types of intramembrane receptor-receptor interactions may have a special role in cotransmission. Such a strong modulation of D_2 receptors has also been found in rat striatal sections when using NT/NN peptides,[25] again emphasizing the importance of intracellular factors and/or of the intact membrane structure. Taken together these studies underline the importance of receptor-receptor interactions exerted at the membrane level between neuropeptide receptors and D_2 receptors, which are determined at least in part by the ongoing activity at D_1 receptors.

It is of interest to note that the switching role of D_1 receptors is abolished when NT and CCK-8 are added jointly to regulate the D_2 receptor binding characteristics in rat neostriatal membranes.[21] Thus, in these experiments threshold concentrations of CCK-8 and NT significantly increased the K_d value of the high-affinity D_2 receptors as studied in competition experiments with the [^{3}H]raclopride versus DA and in saturation experiments involving a D_2 agonist radioligand [^{3}H]NPA. In this case the activation of NT receptors will not allow the activated D_1 receptor to convert the CCK receptor regulation of the D_2 receptors into one of enhancement of the affinity. Instead, the results demonstrate that the reduction of affinity will dominate and that the two neuropeptides synergize in the inhibitory regulation of the D_2 receptor affinity. It becomes increasingly clear that the modulation of D_2 receptor subtype is not dependent upon a single interaction but is determined by a set of directly and indirectly interacting receptors activated by several neurotransmitters impinging on the same striatal cells. The results obtained in the membrane binding studies certainly imply that the same striatal nerve cells must contain both D_1, D_2, NT, and CCK receptors. The cellular colocalization of these receptors, however, still remains to be directly demonstrated.

In conclusion, it seems possible that every neuron operates with a preferred constellation of receptor-receptor interactions, possibly involving the formation of receptor mosaics.[26]

Studies at the Network Level

When using intracerebral microdialysis in combination with studies on DA release, *in vivo* evidence has been obtained that the CCK_B/D_2 antagonistic receptor interaction exists at the presynaptic level in the striatal DA nerve terminal networks.[27] Thus, CCK-8 perfused by the microdialysis probe in the halothane anesthetized rat was able, in a concentration-related way (1 nM to 1 μM), to counteract the inhibitory actions of systemically given apomorphine (0.05 mg/kg, s.c.) on the DA release (FIG. 4), an action blocked by a CCK antagonist. These results seem to give a functional correlate to the antagonistic interaction between CCK_B and D_2 receptors demonstrated in the striatal membrane preparations. Thus, activation of presumable CCK_B receptors may reduce the D_2 autoreceptor affinity leading to a reduction of the apomorphine-induced inhibition of DA release. Studies on GABA release within the nucleus accumbens support the existence of an antagonistic CCK_B/D_2 interaction also within the postsynaptic cells by the demonstration that CCK-8 (1 μM) increased both GABA and DA release by 35 and 43%, respectively.[28] It is also possible to obtain a functional correlate to the synergistic interaction demonstrated between NT and CCK-8 in the control of D_2 receptors.[21] Thus, the two neuropeptides were found to synergistically antagonize the apomorphine-induced inhibition of DA release as evaluated by means of intrastriatal microdialysis. In the presence of 1 nM of CCK-8,

NT in subthreshold concentrations (0.01–1 nM) counteracts the apomorphine (0.05 mg/kg, s.c.) induced inhibition of DA release by 70%, but in the absence of CCK-8, NT in the low concentrations has no action (FIG. 5).

Also in the case of NT/D_2 receptor interactions, it has been possible—by means of intrastriatal and intraaccumbens microdialysis—to obtain a functional correlate to the receptor interactions found in the membrane preparations from the striatum. Thus, the presynaptic NT receptors located on the striatal DA terminals will antagonize the inhibitory actions exerted by apomorphine on DA release mediated by activation of D_2 autoreceptors (FIG. 6).[29] Furthermore, in the awake and unrestrained male rat NT can also antagonize the inhibitory effects of D_2 agonists on extracellular levels of DA, DOPAC, and HVA. These results give evidence that the

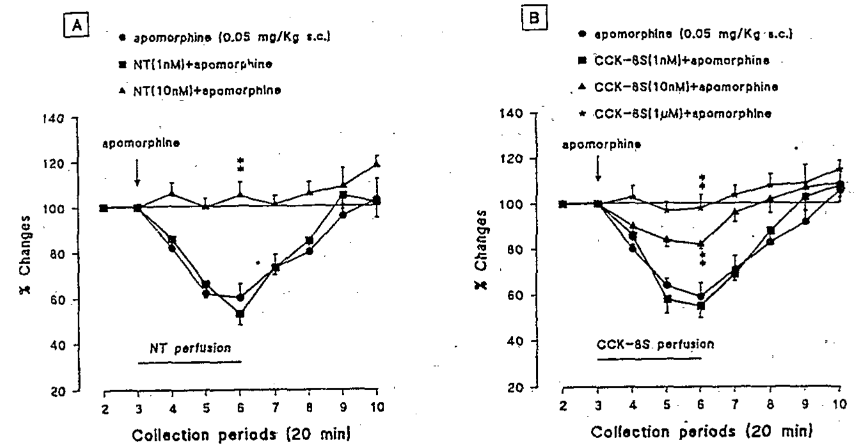

FIGURE 4. Effects of local perfusion with neurotensin (NT) (*panel A*) and CCK-8 (*panel B*) on dopamine (DA) extracellular levels in the dorsal striatal dialysates from the apomorphine-treated halothane anesthetized rat. The results were expressed as a percentage of the mean of three basal values. Mean ± SEM are shown. The absolute value of basal DA outflow was 126 ± 5 fmol/20 min. The statistical analysis was carried out according to one-way ANOVA followed by Newman-Keuls test for multiple comparisons. $^{**}p < 0.01$ versus apomorphine alone and plus 1 nM NT (*panel A*) or 1 nM CCK-8 (*panel B*). Significances are shown only for the peak effect.

presynaptic NT receptors located on DA terminals also can counteract transduction occurring at D_2 autoreceptors leading to inhibition of DA release. Recent studies on D_2-regulated GABA release indicate that D_2 receptors located in the nerve cell membranes on the GABA/enkephalin (ENK) striopallidal neurons projecting to the external globus pallidus are antagonistically regulated by the NT receptors.[11] Thus, in the awake unrestrained male rat perfusion with NT by microdialysis is capable of counteracting the inhibitory actions of the D_2 agonist pergolide on the extracellular levels of GABA. These results provided a functional correlate to the binding experiments postulating the existence of antagonistic NT/D_2 receptor interactions in neostriatal membranes. Thus, the neuroleptic activity of NT peptides[11] and NN peptides[23] may be produced via antagonistic actions on D_2 receptor transduction.

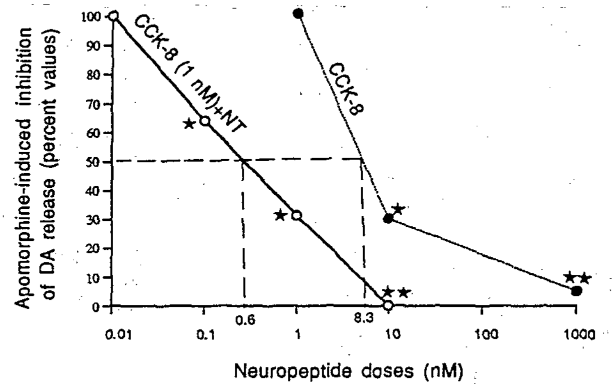

FIGURE 5. Effects of CCK-8 alone or in the presence of increasing concentrations of neurotensin (NT) (0.1, 1, and 10 nM). The area below curves during the perfusion period has been considered (see FIG. 4, curve B) and expressed as percent values of the mean area under the apomorphine curve in the corresponding perfusion period. Concentrations NT and CCK-8 up to 1 nM were by themselves ineffective. Percentage values for NT + CCK-8 and CCK-8 alone have been plotted. From these two dose-response curves an approximate evaluation of the respective ED_{50} values can be obtained as indicated. $n = 5–7$ rats. $^*p < 0.05$; $^{**}p < 0.01$ versus the apomorphine alone group according to one-way ANOVA followed by Neuman-Keuls test for multiple comparisons.

Instead, combined treatment with the D_1 agonist SKF38393 and NT, but not with the D_1 agonist alone, leads to significant increases in the extracellular striatal levels of GABA. In this way the striatal NT receptor can selectively reduce the transmission over the D_2 receptors, leading to a switching of DA transmission towards D_1

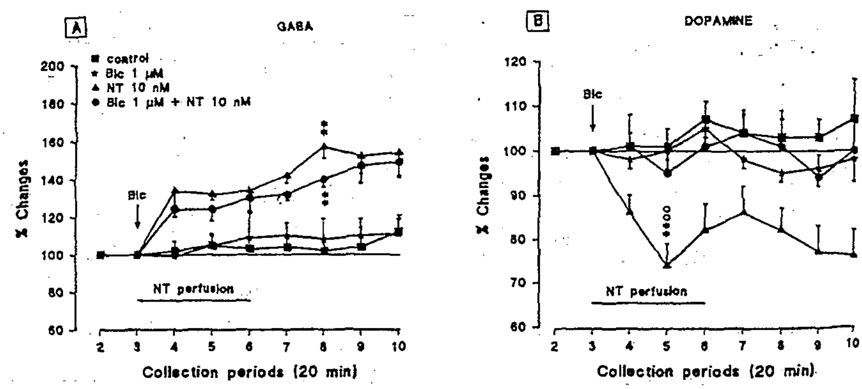

FIGURE 6. Effects of neurotensin (NT) alone and in combination with bicuculline (Bic) on GABA (*panel A*) and dopamine (DA) (*panel B*) extracellular levels from the posteromedial nucleus accumbens of the halothane anesthetized rat. The results are expressed as a percentage of the mean of three basal values. Mean ± SEM are shown. The basal absolute values were 99 ± 6 fmol/20 min for DA and 608 ± 40 fmol/20 min for GABA. $n = 5–7$. $^{**}p < 0.01$ versus control as well as Bic alone. $^*p < 0.01$ versus NT plus Bic.

receptor-mediated neurotransmission, increasing the extracellular GABA levels. Following activation of striatal NT receptors DA transmission will therefore mainly operate via D_1 receptor-mediated excitation of the strionigral GABAergic system.

In this way plastic responses based on receptor diversity and receptor-receptor interactions are made possible for both WT and VT. The data summarized in this paper illustrate these plastic responses for DA neurotransmission, where DA receptor diversity and receptor-receptor interactions among different types of receptors selective for a certain subtype—in this case the D_2 receptor subtype—substantially increase the DA transmission plasticity.

Recently, we focused our attention on the nucleus accumbens, a brain area where the interaction of the two neuropeptides with the DAergic and GABAergic systems also seems to take place. Our results demonstrated that the local perfusion with NT (10 nM) induced a long-lasting increase of basal GABA outflow (+45%), but, surprisingly, produced a prolonged inhibition of DA release (−25%). Pretreatment with the $GABA_A$ antagonist bicuculline (1 μM, a concentration by itself ineffective) abolished the NT-induced reduction of dopamine outflow without affecting the associated increase of GABA release (FIG. 6A and B).[28] These findings provided strong evidence that NT-induced inhibition of DA release is mediated by a local increase in the GABA outflow. The activation of GABA release induced by the peptide could be related to selective postsynaptic antagonistic NT/D_2 receptor-receptor interaction on the GABA neurons innervating the nucleus accumbens.

Taken together, the results obtained with the perfusion of NT in the dorsal striatum and in the nucleus accumbens demonstrate that the neuropeptide differentially influences DA and GABA transmission in these brain areas. Furthermore, they suggest that, in contrast to the dorsal striatum, the presynaptic but not the postsynaptic NT/D_2 receptor-receptor interaction is missing in the nucleus accumbens.[30–32] Thus, it seems possible that the NT-induced activation of GABA release could either directly inhibit the DA release or, indirectly, reduce the activity of a tonic excitatory input on DAergic terminals in the nucleus accumbens. On the contrary, in the dorsal striatum, the lack of DA inhibition could be due to the activation of NT receptors present on the DAergic terminals,[33] which via the presynaptic NT/D_2 receptor interaction increase DA release.

In conclusion, these functional microdialysis data suggest that the modulation by NT and CCK-8 of the striatal and accumbens DAergic and GABAergic systems may be relevant for the postulated antipsychotic actions of these neuropeptides.[34,35]

CCK_B/D_2 AND NT/D_2 RECEPTOR INTERACTIONS AND THEIR RELEVANCE FOR SCHIZOPHRENIA

The present studies open up the possibility that the neuroleptic-like actions seen following central NT and CCK-8 administration is the result of an antagonistic NT and CCK_B receptor modulation of the postsynaptic D_2 receptors in the neostriatum and the nucleus accumbens.[18,36] These antagonistic intramembrane interactions involving the postsynaptic D_2 receptors probably take place in the striopallidal GABAergic neurons involving both the dorsal and ventral components of this pathway, the ventral component being of particular interest in relation to schizophrenia in view of its role in controlling the output from the limbic system. Thus, it may be surmised that schizophrenia can be the final outcome of different neurochemical lesions such as alterations in CCK-8 and/or NT release, as well as in CCK and NT receptor interactions with the D_2 receptors. These alterations could lead to a pathological pattern in DA communication (WT and VT). However, abnormal spatial/temporal patterns in the DA communication may also depend on a miswiring

of the system inasmuch as structural abnormalities have been described in the brain of some patients with schizophrenia.[11,37,38]

This new way of looking at schizophrenia may represent a more precise picture of the pathogenetic mechanisms and it may also suggest novel therapeutic approaches.

SUMMARY

Receptor diversity in combination with receptor-receptor subtype specific interactions, which can be antagonistic or synergistic in character, markedly increase plasticity in WT and VT in the nervous system. In this way switching among transmission lines for the various DA receptor subtypes becomes possible. Some of these aspects are supported by our work on selective modulation of D_2 receptors by CCK and NT. Selective regulation of D_2 receptors via CCK-8 receptor subtypes and NT receptors may underlie CCK/DA interactions and NT/DA interactions in the basal ganglia. These studies underline the importance of receptor-receptor interactions exerted at the membrane level between neuropeptide receptors and D_2 receptors, which are determined at least in part by the ongoing activity at D_1 receptors. In the case of both CCK/D_2 and NT/D_2 receptor interactions, it has been possible, by means of intrastriatal and intraaccumbens microdialysis, to obtain a functional correlate to the receptor interactions found in the membrane preparations from the striatum.

Schizophrenia may be in part related to reduced release of CCK and/or NT peptides or to alterations in their receptor interactions with the D_2 receptor. This view may lead to new therapeutic approaches.

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